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# Highly efficient chiral polydentate sulfinyl ligands/catalysts containing prolinol moiety

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ABSTRACT

New polydentate chiral ligands, containing the hydroxyl group, stereogenic sulfinyl group and enantiomeric prolinol moieties were synthesized and proved very efficient catalysts in the asymmetric diethylzinc addition to benzaldehyde, the asymmetric aldol condensation and the asymmetric Mannich reaction. Replacement of the central hydroxyl group with the second prolinol moiety of the same absolute configuration gave new ligands in which the sulfinyl group was not a stereogenic centre anymore, but which proved almost equally efficient as catalysts for the reactions investigated. The absolute configuration of the proline moiety exerted a decisive impact on the stereochemical outcome of these reactions, deciding about the absolute configuration of the products formed.



## 1. Introduction

A search for new organocatalysts for the stereoselective formation of optically active compounds is one of the most important and challenging tasks of contemporary asymmetric synthesis. The main advantage of using organocatalysts in asymmetric synthesis is the ability to avoid toxic and expensive metals complexes.

Our recent works have been focused on the preparation of enantiopure heteroatom-containing compounds that could be used as chiral ligands or catalysts in the asymmetric C–C bond formation. We have succeeded in the chemoenzymatic synthesis of a variety of ligands **4**, containing a stereogenic sulfinyl moiety, an enantiomeric amine fragment and the hydroxyl group (Scheme 1).[1] The crucial step was the *Candida antarctica* lipase (CAL-B)-promoted desymmetrization of prochiral bis(2-hydroxymethylphenyl) sulfoxide **1**, which allowed us to obtain the desired precursor—monoacetate **2** in one step in a high yield (98%) and in an almost enantiomerically pure form. Simple ensuing chemical transformations, consisting of mesylation of the hydroxyl group to give **3**, followed by the reaction with a relevant amine and removal of the acetyl group, led to ligands **4**, which proved to be excellent catalysts in various reactions of asymmetric synthesis.

Thus, the ligands bearing enantiomeric primary amine moieties (**4a**–**f**) proved particularly efficient catalysts in aldol,[2] nitroaldol (Henry),[3,4] aza-Henry[5] and Mannich[6] reactions, while those bearing enantiomeric aziridine moieties (**4h**–**j**)—in the reactions involving organozinc reagents, i.e., in the asymmetric organozinc additions to aldehydes,[7,8] the Michael diethylzinc additions to enones[9] and the Simmons – Smith cyclopropanation of allyl alcohols.[10] In all cases the products were obtained in the yields up to 98% and with ee's up to 98%. It was found by us that the absolute configuration of the amine substituent exerted a decisive impact on the stereochemical outcome of the reactions and, hence, on the absolute configuration of the products, with only a small 'match–mismatch' effect caused by the chirality of the sulfinyl group. Nevertheless, the presence of all the coordinating centers, i.e., the hydroxyl, sulfinyl groups and the amine nitrogen atom, was proven to be essential for the efficiency of the catalysts and allowed us to conclude that the ligands **4** demonstrated a tridentate character.[4,6] Particularly, the presence of the stereogenic sulfinyl group proved crucial for the outcome of all the reactions since its replacement with the corresponding sulfide or sulfone moiety resulted in a substantial decrease of both the yield and enantiomeric excess of the products. Interestingly, the hydroxyl group in **4** could be replaced by the identical enantiomeric amine moiety, but in order to achieve high catalytic activity of the newly formed

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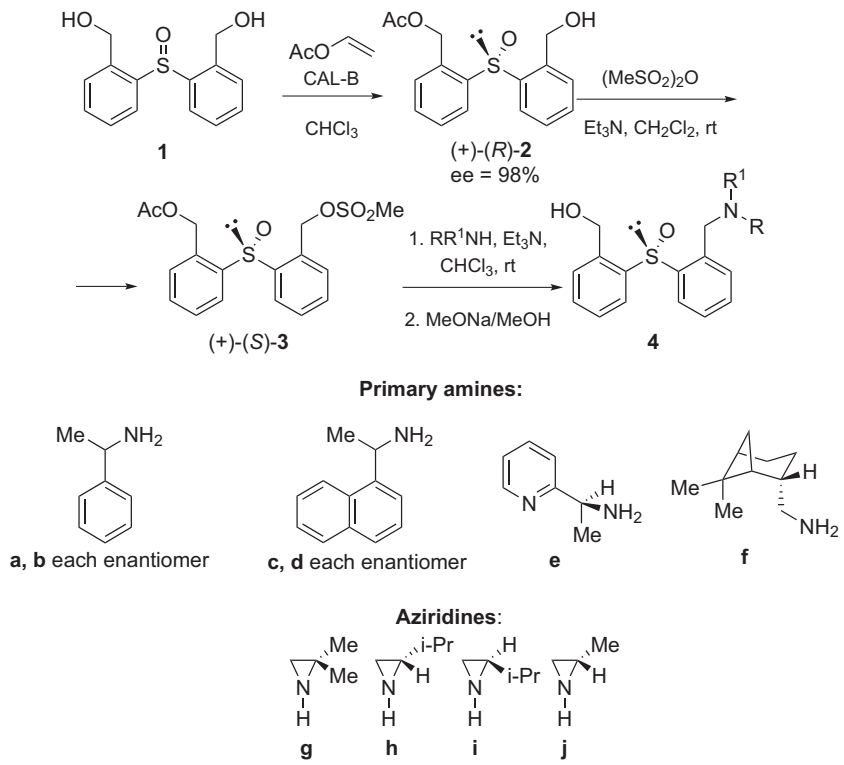



**Scheme 1.** Synthesis of sulfinyl ligands **4.**

ligand **5** (Fig. 1) and stereoselectivity of the reactions in which it was used as catalyst, it was necessary to retain in its molecule the sulfinyl moiety, even if the latter lost in this case its stereogenic character.[4,6]

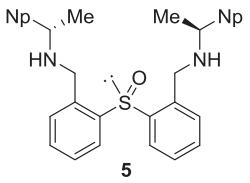



**Fig. 1.** The diamino analog of ligand **4d.**

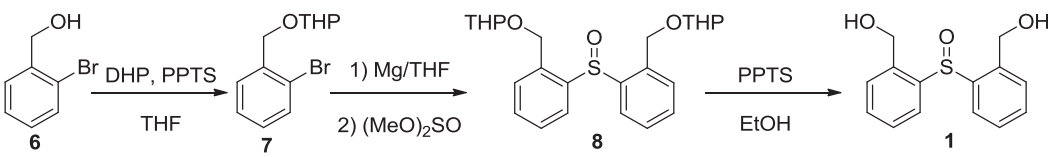
Looking for other chiral amine-type substituents that could be useful in the designing of new ligands we focused our attention on prolinol, which seemed particularly interesting due to the presence of the hydroxyl group, capable of acting as an additional coordinating centre. In this context it should be mentioned that proline and its analogs are widely used as chiral organocatalysts.[11] Particularly, prolinol and its various derivatives are commonly applied in asymmetric synthesis.[12] They proved to be valuable auxiliaries[13] and catalysts in the asymmetric formation of carbon−carbon[14] and carbon-heteroatom bonds.[15] Therefore, we decided to replace the amino groups in our original sulfinyl ligands **4** and **5** with one or two prolinol moieties, to obtain new ligands **9** and **10**, having four or five potential coordination centers, respectively (Scheme 3).

## 2. Results and discussion

### 2.1. Synthesis of ligands

We attempted to synthesize the basic substrate, namely bis(2-hydroxymethylphenyl) sulfoxide **1**, in a different way than that originally described.[1] We started from *o*-bromobenzyl alcohol **6**, in which the hydroxyl group was protected with dihydropyran (DHP), according to the literature procedure,[16] to give **7** in 98% yield. In the next step the protected alcohol was transformed into a Grignard reagent and treated with dimethyl sulfite to yield **8** (83.7%), followed by the removal of the tetrahydropyranyl group (THP) with pyridinium *p*-toluenesulfonate (PPTS) to give the desired compound **1** (86.5%) (Scheme 2). The overall yield of **1** achieved using the present method was higher than using the one previously described.[1]

Synthesis of ligands/catalysts **9a** and **9b**, with a stereogenic sulfur atom, was carried out according to the procedure previously described (Scheme 1),[1] by enzymatic desymmetrization of the sulfoxide **1**, mesylation of the hydroxyl group, reaction with (*S*)-prolinol or (*R*)-prolinol, respectively, and removal of the acetyl group with sodium methoxide. In turn, the ligands/catalysts **10a**




**Scheme 2.** Synthesis of prochiral bis(2-hydroxymethylphenyl) sulfoxide **1.**